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Recipient Comorbidity and Survival Outcomes After Kidney Transplantation: A UK-wide Prospective Cohort Study

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Background. Comorbidity is increasingly common in kidney transplant recipients, yet the implications for transplant outcomes are not fully understood. We analyzed the relationship between recipient comorbidity and survival outcomes in a UK-wide prospective cohort study—Access to Transplantation and Transplant Outcome Measures (ATTOM). **Methods.** A total of 2100 adult kidney transplant recipients were recruited from all 23 UK transplant centers between 2011 and 2013. Data on 15 comorbidities were collected at the time of transplantation. Multivariable Cox regression models were used to analyze the relationship between comorbidity and 2-year graft survival, patient survival, and transplant survival (earliest of graft failure or patient death) for deceased-donor kidney transplant (DDKT) recipients (n = 1288) and living-donor kidney transplant (LDKT) recipients (n = 812). **Results.** For DDKT recipients, peripheral vascular disease (hazard ratio [HR] 3.04, 95% confidence interval [CI]: 1.37-6.74; $P = 0.006$) and obesity (HR 2.27, 95% CI: 1.27-4.06; $P = 0.006$) were independent risk factors for graft loss, while heart failure (HR 3.77, 95% CI: 1.79-7.95; $P = 0.0005$), cerebrovascular disease (HR 3.45, 95% CI: 1.72-6.92; $P = 0.0005$), and chronic liver disease (HR 4.36, 95% CI: 1.29-14.71; $P = 0.018$) were associated with an increased risk of mortality. For LDKT recipients, heart failure (HR 3.83, 95% CI: 1.15-12.81; $P = 0.029$) and diabetes (HR 2.23, 95% CI: 1.03-4.81; $P = 0.042$) were associated with poorer transplant survival. **Conclusions.** The key comorbidities that predict poorer 2-year survival outcomes after kidney transplantation have been identified in this large prospective cohort study. The findings will facilitate assessment of individual patient risks and evidence-based decision making.

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INTRODUCTION

Kidney transplantation is widely regarded as the treatment of choice for end-stage renal disease (ESRD). However, outcomes after transplantation vary considerably between patients and prediction of individual risk is challenging due to the increasing prevalence of complex comorbidity among the ESRD population. Conditions such as diabetes, hypertension, and obesity, which contribute to the development of ESRD, are on the rise,[1] while ESRD itself is an important risk factor for other comorbidities such as cardiovascular disease.[2,3] Over the past decade, the proportion

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of deceased-donor kidney transplant (DDKT) recipients >60 years of age has increased from 17% to 29% in the UK,[4] and the burden of comorbidity among patients undergoing kidney transplantation has also risen significantly.[5-7]

Despite this, there are limited data on the impact of comorbidity on transplant outcomes. A small number of studies have demonstrated the overall detrimental effect of comorbidity on transplant outcomes using various comorbidity indices.[5,8-10] However, this does not allow characterization of the risks associated with specific comorbid conditions. Retrospective registry analyses have identified several comorbidities as risk factors for transplant outcomes, but the results show considerable heterogeneity and are limited by the reliability of the data.[11-13] Up-to-date and reliable evidence is essential to enable clinicians to fully inform patients of their individual risks and likely outcomes, thereby facilitating shared decision-making and informed consent.

We conducted a national prospective cohort study to investigate the impact of a wide range of baseline comorbid conditions on survival outcomes following kidney transplantation. We report the 2-year survival outcomes of the study, which was conducted as part of the Access to Transplantation and Transplant Outcome Measures (ATTOM) research programme.

MATERIALS AND METHODS

Study Design and Participants

ATTOM is a national prospective cohort study investigating the factors that influence access to and outcomes from renal transplantation in the UK. A full description of the ATTOM protocol has been reported previously.[14] A cohort of 2262 incident kidney transplant recipients were recruited to ATTOM at the time of transplantation, from all 23 UK renal transplant centers. In each center, recruitment took place over a 12-month period between November 1, 2011 and March 31, 2013. Patients aged 18–75 years were eligible for recruitment. For the purposes of this analysis, multiorgan transplant recipients (n = 162) were excluded. The final study sample (n = 2100) represented 73% of eligible study participants from the national kidney-only transplant population (Figure 1). Patients were followed up for 2 years from the date of transplant. DDKT recipients (n = 1288) and living-donor kidney transplant (LDKT) recipients (n = 812) were analyzed separately.

Data Variables

The variables of interest were recipient comorbidities at the time of transplantation comprising diabetes, ischemic heart disease (IHD), heart failure (HF), atrial fibrillation, cardiac valve replacement, pacemaker, cerebrovascular disease (CVD), peripheral vascular disease (PVD), abdominal aortic aneurysm, chronic respiratory disease, chronic liver disease (CLD), blood borne viruses, malignancy, mental illness (definitions given in **Table S1, SDC**, http://links.lww.com/TP/B802), and body mass index (BMI).

The primary outcome measures were graft survival, patient survival, and transplant survival. Graft survival was defined as the time from transplantation to graft failure (earliest of return to dialysis or retransplantation), with censoring for death with a functioning graft, at last follow-up or at 2 years. Patient survival was defined as the time from transplantation to patient death, with censoring at last follow-up or at 2 years. Transplant survival is a composite outcome defined as the time from transplantation to the earliest of graft failure or patient death, with censoring at last follow-up or at 2 years.

Potential confounders considered in multivariable analyses included (a) recipient variables: age, gender, ethnicity, primary renal disease (as classified by ERA-EDTA codes[15]), time on dialysis, previous transplantation, sensitization level, smoking status; (b) donor variables: age, gender, ethnicity, BMI; (c) transplant variables: HLA mismatches (MM), cold ischemia time, delayed graft function (DGF).

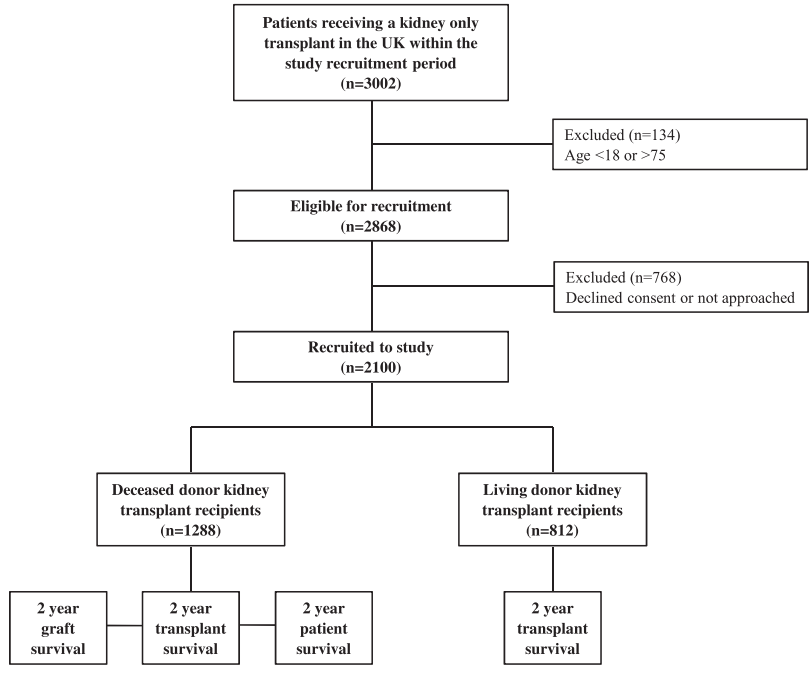

FIGURE 1. Study population and analyses. Patients were recruited from all 23 UK renal transplant centers. Recruitment took place over a 12-mo period in each center, between November 1, 2011, and March 31, 2013.

Ethnicity was coded as White, Black, Asian, and Other (including Chinese and mixed origin). Recipient calculated reaction frequency (cRF) ≥85% was used to define highly sensitized recipients. The cRF is the percentage of a pool of 10 000 UK donors to whom the recipient has unacceptable HLA antibodies. HLA mismatches were classified into 4 levels as defined by the current UK deceased-donor kidney allocation scheme: level 1 (000 HLA-A, B, DR MM), level 2 (0DR + 0/1B MM), level 3 (0DR + 2B MM) or (1DR + 0/1B MM), and level 4 (1DR + 2B MM) or (2DR MM).[16]

Data Collection

Baseline recipient variables (including comorbidity) were collected by trained research nurses at the time of transplantation from patient interviews, case notes, local electronic patient information systems, and/or confirmed with the patient's named consultant nephrologist. Independent validation of 5% of data entries in all research sites confirmed >98% concordance for all data fields.[14] Donor and transplant variables and 2-year graft and patient survival data were obtained through linkage with the UK Transplant Registry.

Statistical Methods

Baseline characteristics were compared with χ^2 tests for categorical data and Mann-Whitney U tests for nonparametric continuous data. The impact of comorbidity on 2-year survival outcomes was examined using Kaplan-Meier estimates and Cox proportional hazards regression models. DDKT and LDKT recipients were analyzed separately. As there were no significant differences in outcomes between recipients of donors after circulatory death and donors after brain death, all DDKT recipients were analyzed together. For DDKT recipients, separate multivariable models were built for the 3 different outcomes of transplant, graft, and patient survival. For LDKT recipients, modelling was only possible for transplant survival, as the lower number of graft failures and patient deaths prevented modelling of graft and patient survival separately. All comorbidities were considered for inclusion in the multivariable models, and those leading to a significant ($P < 0.05$) change in log likelihood were retained using a manual backward elimination method. Models were adjusted for statistically significant variables as well as variables selected a priori on the basis of clinical relevance. Continuous variables were explored as linear, fractional polynomials and categorical variables. In all models, the effect of the time on dialysis variable was only found to be significant after 3 years, and thus it was converted to a binary variable (<3 y versus ≥3 y) as this provided the best fit in each model. The relationship between recipient BMI and graft survival was also found to be better represented by converting BMI to a categorical variable, in accordance with the World Health Organization (WHO) BMI classifications.[17] Potential interactions between all variables were tested; none were significant. The proportional hazards assumption was found to be satisfied for all variables after checking log cumulative hazards plots and Schoenfeld residuals. Frailty models were used to check for intercenter variation by using the likelihood ratio test to assess the change in –2LogL after inclusion of transplant center as a random effect. The adjusted risk difference (ARD) was calculated using methods described by Laubender et al.[18] The ARD describes the absolute effect of the comorbidity risk factor on survival probabilities after adjustment for covariates in the multivariable model. Standard errors (SE) of the ARD were derived from bootstrap methods using 1000 resamples of the data. Patients with missing data were excluded, the extent of missing data is shown in **Table S2** (**SDC**, http://links.lww.com/TP/B802). Sensitivity analyses were conducted to test robustness of the results; each model was adjusted for a risk score developed from UK Transplant Registry data for kidney transplants performed in the 5 years before the study recruitment period (2006–2011), rather than adjusting for individual confounding factors. This minimized the number of degrees of freedom (*df*) in the models, and enabled checking for any missed comorbidity effects. All analyses were conducted using SAS 9.4 (SAS Institute Inc, Cary, USA).

Ethics Approval

East of England Research Ethics Committee (reference number 11/EE/0120).

RESULTS

Baseline Characteristics

Characteristics of the DDKT (n = 1288) and LDKT (n = 812) recipients, donors, and transplants are shown in Table 1. These were consistent with UK Transplant Registry data for the study recruitment period.[19,20] The demographics of recruited versus excluded patients were compared (**Table S3**, **SDC**, http://links.lww.com/TP/B802). There was a higher proportion of White patients in the recruited group compared with the excluded group; however, there were no significant differences in age group, gender, or type of transplant. Table 2 shows the prevalence of comorbidity in the study cohort at the time of transplantation. DDKT recipients had significantly higher rates of diabetes (16.0% versus 10.3%, $P = 0.0002$), IHD (9.8% versus 7.0%, $P = 0.029$), HF (3.1% versus 1.6%, $P = 0.033$), CVD (5.8% versus 3.1%, $P = 0.004$), and PVD (3.3% versus 1.7%, $P = 0.027$) compared with LDKT recipients.

DDKT Recipients

Transplant Survival

Overall, there were 134 "transplant failures" (85 graft failures and 49 patient deaths). The Kaplan-Meier estimate for 2-year transplant survival was 89.4% (95% confidence interval [CI]: 87.6-91.0). After adjustment for relevant factors in the multivariable Cox regression model, HF (HR 2.39, 95% CI: 1.30-4.37; $P = 0.005$) and CVD (HR 2.33, 95% CI: 1.40-3.88; $P = 0.001$) were associated with a significant increase in the risk of transplant failure (Table 3). There was no significant intercenter variation in transplant survival when including transplant center as a random effect in the model (difference in –2LogL = 0.02, $df = 1$, $P = 0.885$). For HF, the ARD was 0.117 (SE 0.052) (ie, patients with heart failure had an 11.7% increased risk of transplant failure within 2 years compared to those without heart failure, after adjustment for all other factors in the multivariable model). For CVD, the ARD was 0.101 (SE 0.043). The effect of adding DGF to the final model is shown in **Table S4** (**SDC**, http://links.lww.com/TP/B802).

TABLE 1.
Characteristics of the study cohort

Variables	DDKT recipients n = 1288	LDKT recipients n = 812	*P*
Recipient variables			
Recipient age, y (median, IQR)	54 (44–63)	46 (34–56)	<0.0001
Recipient age group, y (n, %)			<0.0001
18–34	132 (10.3)	229 (28.2)	
35–49	369 (28.7)	263 (32.4)	
50–64	543 (42.2)	252 (31.0)	
65–75	244 (18.9)	68 (8.4)	
Recipient gender (n, %)			0.267
Male	824 (64.0)	500 (61.6)	
Female	464 (36.0)	312 (38.4)	
Recipient ethnicity (n, %)			0.0002
White	1023 (79.7)	707 (87.1)	
Asian	140 (10.9)	62 (7.6)	
Black	96 (7.5)	35 (4.3)	
Other	25 (2.0)	8 (1.0)	
Primary renal disease (n, %)			<0.0001
Polycystic kidney disease	219 (17.0)	112 (13.9)	
Diabetic nephropathy	134 (10.4)	48 (5.9)	
Glomerulonephritis	320 (24.9)	232 (28.7)	
Pyelonephritis	138 (10.7)	128 (15.8)	
Hypertensive nephropathy	89 (6.9)	37 (4.6)	
Renal vascular disease	29 (2.3)	9 (1.1)	
Other	163 (12.7)	85 (10.5)	
Uncertain	194 (15.1)	157 (19.4)	
Time on dialysis (n, %)			<0.0001
Pre-emptive	137 (10.6)	279 (34.4)	
0–1 y	160 (12.4)	198 (24.4)	
1–3 y	366 (28.4)	185 (22.8)	
3–5 y	295 (22.9)	78 (9.6)	
>5 y	330 (25.6)	72 (8.9)	
Previous transplant (n, %)	165 (12.9)	117 (14.5)	0.297
Highly sensitized, cRF ≥ 85% (n, %)	126 (9.8)	95 (11.7)	0.163
Smoking status (n, %)			0.702
Nonsmoker	137 (11.7)	78 (10.7)	
Ex-smoker	325 (27.7)	212 (29.2)	
Smoker	710 (60.6)	437 (60.1)	
Donor variables			
Donor age, y (median, IQR)	54 (43–64)	48 (39–57)	<0.0001
Donor age group, y (n, %)			<0.0001
<18	31 (2.4)	0	
18–34	160 (12.4)	143 (17.6)	
35–49	303 (23.5)	298 (36.7)	
50–64	512 (39.8)	308 (37.9)	
65–75	234 (18.2)	61 (7.5)	
>75	48 (3.7)	2 (0.3)	
Donor gender (n, %)			0.001
Male	696 (54.0)	379 (46.7)	
Female	592 (46.0)	432 (53.3)	
Donor ethnicity (n, %)			<0.0001
White	1208 (95.2)	720 (88.7)	
Asian	21 (1.7)	52 (6.4)	
Black	23 (1.8)	28 (3.5)	
Other	17 (1.3)	12 (1.5)	

Continued next page

TABLE 1 (CONTINUED).

Characteristics of the study cohort

Variables	DDKT recipients n = 1288	LDKT recipients n = 812	*P*
Donor BMI, kg/m^2 (n, %)			<0.0001
Underweight (<18.5)	0	0	
Normal (18.5–24.9)	463 (37.3)	254 (32.9)	
Overweight (25.0–29.9)	494 (39.7)	390 (50.5)	
Obese (≥30.0)	286 (23.0)	128 (16.6)	
Transplant variables			
HLA MM level (n, %)			<0.0001
1	155 (12.0)	91 (11.2)	
2	355 (27.6)	105 (12.9)	
3	679 (52.7)	360 (44.3)	
4	99 (7.7)	256 (31.5)	
CIT, h (median, IQR)	14.5 (11.4–17.3)	3.3 (2.4–4.1)	<0.0001
Delayed graft function (n, %)	378 (31.1)	30 (3.9)	<0.0001

Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in **Table S2** (**SDC**, http://links.lww.com/TP/B802).
BMI, body mass index; CIT, cold ischemia time; cRF, calculated reaction frequency; DDKT, deceased-donor kidney transplant; HLA MM, HLA mismatch; IQR, interquartile range; LDKT, living-donor kidney transplant.

TABLE 2.

Prevalence of recipient comorbidity

	DDKT recipients n = 1288	LDKT recipients n = 812	*P*
Diabetes (n, %)	205 (16.0)	83 (10.3)	0.0002
Ischemic heart disease (n, %)	126 (9.8)	57 (7.0)	0.029
Heart failure (n, %)	40 (3.1)	13 (1.6)	0.033
Atrial fibrillation (n, %)	25 (1.9)	12 (1.5)	0.434
Cardiac valve replacement (n, %)	10 (0.8)	8 (1.0)	0.609
Pacemaker (n, %)	10 (0.8)	5 (0.6)	0.673
Cerebrovascular disease (n, %)	75 (5.8)	25 (3.1)	0.004
Peripheral vascular disease (n, %)	43 (3.3)	14 (1.7)	0.027
Abdominal aortic aneurysm (n, %)	4 (0.3)	2 (0.3)	0.790
Chronic respiratory disease (n, %)	108 (8.4)	59 (7.3)	0.359
Chronic liver disease (n, %)	25 (1.9)	14 (1.7)	0.722
Blood borne viruses (n, %)	38 (3.0)	13 (1.6)	0.051
Malignancy (n, %)	93 (7.2)	49 (6.1)	0.294
Mental illness (n, %)	75 (5.8)	41 (5.1)	0.453
BMI, kg/m^2 (n, %)			0.121
Underweight (<18.5)	26 (2.1)	23 (3.0)	
Normal (18.5–24.9)	461 (37.5)	312 (40.8)	
Overweight (25.0–29.9)	462 (37.6)	282 (36.9)	
Obese (≥30.0)	281 (22.9)	147 (19.2)	
Number of comorbidities (n, %)			0.002
0	573 (46.7)	414 (54.4)	
1–2	579 (47.2)	316 (41.5)	
≥3	74 (6.0)	31 (4.1)	

BMI, body mass index; DDKT, deceased-donor kidney transplant; LDKT, living-donor kidney transplant.
Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in **Table S2**.

Graft Survival

At 2 years, there were 85 graft failures, and the Kaplan-Meier estimate of graft survival was 93.2% (95% CI: 91.7-94.5). Multivariable Cox regression modelling showed PVD (HR 3.04, 95% CI: 1.37-6.74; *P* = 0.006) and obesity (BMI ≥ 30.0) (HR 2.27, 95% CI: 1.27-4.06; *P* = 0.006, compared with normal BMI 18.5–24.9) to be independent risk factors for graft loss (Table 3). The obesity variable was explored further in the model by dividing it into class I and class II and above (BMI 30.0–34.9 and ≥35.0, respectively) (**Table S5**, **SDC**, http://links.lww.com/TP/B802). There were too few patients with obesity class III (BMI ≥ 40.0) (n = 7) to include this as a separate category. There was no significant variation in the risk of graft failure for the different classes of obesity; therefore, the broader category of obesity (BMI ≥ 30.0) was retained in the main

TABLE 3.

Cox regression analysis for impact of comorbidity on 2-y survival outcomes of deceased donor kidney transplants

	Transplant survival model		Graft survival model		Patient survival model	
Variables	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Recipient comorbidity						
Heart failure	2.39 (1.30-4.37)	0.005	–	–	3.77 (1.79-7.95)	0.0005
Cerebrovascular disease	2.33 (1.40-3.88)	0.001	–	–	3.45 (1.72-6.92)	0.0005
Chronic liver disease	–	–	–	–	4.36 (1.29-14.71)	0.018
Peripheral vascular disease	–	–	3.04 (1.37-6.74)	0.006	–	-
BMI, kg/m^2						
Underweight (<18.5)	–	–	0.86 (0.11-6.49)	0.885	–	-
Normal (18.5–24.9)	–	–	1 (reference)		–	-
Overweight (25.0–29.9)	–	–	1.48 (0.84-2.61)	0.180	–	-
Obese (≥30.0)	–	–	2.27 (1.27-4.06)	0.006	–	-
Other variables						
Time on dialysis (y)						
<3	1 (reference)		1 (reference)		1 (reference)	
≥3	2.08 (1.41-3.08)	0.0002	1.84 (1.11-3.04)	0.018	2.47 (1.36-4.50)	0.003
Recipient age (per 10 y)	1.10 (0.92-1.30)	0.290	0.84 (0.68-1.05)	0.128	1.67 (1.23-2.25)	0.0009
Recipient ethnicity						
White	1 (reference)		1 (reference)		–	-
Asian	0.67 (0.35-1.29)	0.228	0.76 (0.35-1.69)	0.504	–	-
Black	1.23 (0.68-2.21)	0.495	1.52 (0.77-3.02)	0.228	–	-
Other	0.37 (0.05-2.63)	0.317	0.62 (0.08-4.53)	0.636	–	-
Highly sensitized (cRF ≥ 85%)	1.47 (0.87-2.47)	0.153	2.22 (1.18-4.19)	0.014	–	-
Donor age (per 10 y)	1.14 (0.99-1.31)	0.066	1.23 (1.02-1.48)	0.028	1.11 (0.89-1.39)	0.349
HLA MM level						
1	1 (reference)		1 (reference)		1 (reference)	
2	1.18 (0.62-2.27)	0.612	2.94 (1.08-7.98)	0.035	0.40 (0.16-1.01)	0.052
3	1.05 (0.57-1.94)	0.866	2.25 (0.85-5.93)	0.103	0.46 (0.21-1.01)	0.051
4	1.25 (0.53-2.93)	0.612	2.78 (0.81-9.59)	0.106	0.66 (0.22-2.01)	0.467
Cold ischemia time (per h)	1.04 (1.01-1.08)	0.028	1.01 (0.97-1.06)	0.568	1.04 (0.99-1.10)	0.118

BMI, body mass index; CI, confidence interval; cRF, calculated reaction frequency; HLA MM, HLA mismatch; HR, hazard ratio.

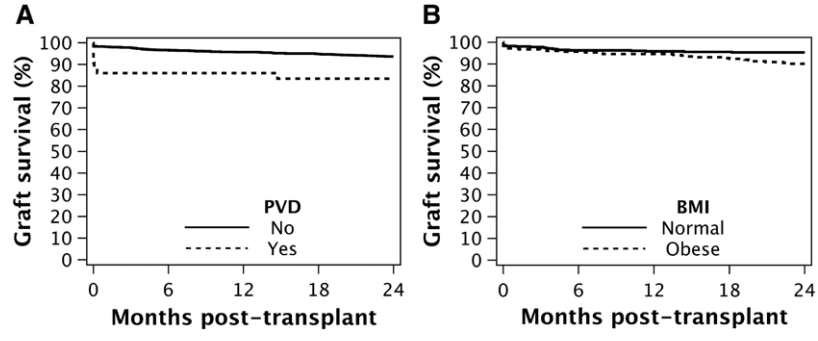

FIGURE 2. Kaplan-Meier curves for 2-y graft survival of deceased-donor kidney transplants. A, Peripheral vascular disease (PVD). B, Body mass index (BMI).

model (Table 3). No center effect on graft survival was found when modelling center as a random effect (difference in –2LogL = 0.23, *df* = 1, *P* = 0.632). Among patients with PVD, the risk of graft failure was highest in the first 10 days following transplantation, as demonstrated by the initial steep drop in the survival curve before the more gradual decline (Figure 2A); 85.7% graft failures in the PVD group occurred during this early postoperative period, compared with 26.9% among patients without PVD. In contrast, the impact of obesity on graft survival followed a more gradual decline over the 2-year period (Figure 2B). Unadjusted 2-year graft survival estimates for patients with and without PVD and obesity are shown in Table 4. The ARD for PVD was 0.104 (SE 0.058) and for obesity was 0.060 (SE 0.029). The incidence of delayed graft function was 31.1% for all patients, 48.7% for patients with PVD, and 39.1% for patients with obesity. Adding DGF to the final model resulted in a reduction in the effect of PVD (**Table S4, SDC**, http://links.lww.com/TP/B802). The cause of graft failure for all patients as well as patients with PVD and obesity in the DDKT cohort is shown in Table 5.

TABLE 4.

Kaplan-Meier estimates for 2-y graft survival of deceased-donor kidney transplants

Comorbidity	Survival (95% CI)	*P*
Peripheral vascular disease		0.006
No	93.6 (92.0-94.8)	
Yes	83.5 (68.5-91.8)	
BMI, kg/m^2		0.012
Normal (18.5–24.9)	95.2 (92.7-96.8)	
Obese (≥30.0)	90.1 (85.9-93.1)	

Data are missing for some participants and excluded from percentage calculations. Number of missing data are shown in Table S2 (SDC, http://links.lww.com/TP/B802).
P-value is for log-rank test.
BMI, body mass index; CI, confidence interval.

TABLE 5.

Cause of graft failure among DDKT cohort

Cause of graft failure	All patients	Obese patients	PVD patients
Acute rejection	26 (34.2%)	11 (44.0%)	1 (14.3%)
Vascular thrombosis	6 (7.9%)	0 (0%)	1 (14.3%)
Technical operative issues	9 (11.8%)	3 (12.0%)	3 (42.9%)
Nonviable kidney	9 (11.8%)	3 (12.0%)	1 (14.3%)
Infection	1 (1.3%)	0 (0%)	0 (0%)
Recurrent primary renal disease	4 (5.3%)	0 (0%)	0 (0%)
Other	21 (27.6%)	8 (32.0%)	1 (14.3%)

DDKT, deceased-donor kidney transplant; PVD, Peripheral vascular disease.

Patient Survival

There were 56 patient deaths, of which 49 were deaths with a functioning graft. The 2-year Kaplan-Meier survival estimate was 95.4% (95% CI: 94.1-96.5). The comorbidities significantly associated with inferior patient survival in the multivariable model included HF (HR 3.77, 95% CI: 1.79-7.95; $P = 0.0005$), CVD (HR 3.45, 95% CI: 1.72-6.92, $P = 0.0005$), and CLD (HR 4.36, 95% CI: 1.29-14.71; $P = 0.018$) (Table 3). There were no significant center differences in patient survival (difference in –2LogL = 0.01, $df = 1$; $P = 0.925$). Among patients with HF and CVD, just over half of patient deaths occurred in the second year after transplantation (55.6% and 58.3%, respectively), while 100% of deaths among patients with CLD occurred within the first year posttransplantation. This is demonstrated by the survival curves in Figure 3A–C. Unadjusted 2-year patient survival estimates for patients with and without HF, CVD, and CLD are shown in Table 6. For HF, CVD, and CLD, the ARD was 0.159 (SE 0.057), 0.041 (SE 0.027), and 0.056 (SE 0.091), respectively. The effect of adding DGF to the final model is shown in **Table S4** (**SDC**, http://links.lww.com/TP/B802).

TABLE 6.

Kaplan-Meier estimates for 2-y patient survival after deceased-donor kidney transplantation

Comorbidity	Survival (95% CI)	*P*
Heart failure		<0.0001
No	96.0 (94.8-97.0)	
Yes	75.8 (58.5-86.7)	
Cerebrovascular disease		<0.0001
No	96.2 (94.9-97.1)	
Yes	82.7 (71.5-89.8)	
Chronic liver disease		0.003
No	95.7 (94.3-96.7)	
Yes	83.6 (62.0-93.5)	

P-value is for log-rank test.
CI, confidence interval.

LDKT Recipients

In the LDKT cohort, it was only possible to model transplant survival, as the smaller number of recipients and outcome events prevented meaningful analysis of separate graft and patient survival models. There were 42 "transplant failures" (26 graft failures and 16 patient deaths). The Kaplan-Meier estimate for transplant survival at 2 years was 94.7% (95% CI: 92.9-96.0). The multivariable model demonstrated significantly higher risk of transplant failure for HF (HR 3.83, 95% CI: 1.15-12.81; $P = 0.029$) and diabetes (HR 2.23, 95% CI: 1.03-4.81; $P = 0.042$) (Table 7). There was no significant center effect on LDKT transplant survival (difference in –2LogL = 0.11, $df = 1$; $P = 0.741$). The ARD for HF was 0.121 (SE 0.099) and for diabetes was 0.056 (SE 0.036).

Sensitivity Analyses

Each multivariable model was checked by adjusting for a risk score (Boxes S1, S2, S3, and S4) rather than entering the confounding factors individually into the model (**Tables S6**, **S7**, **S8**, and **S9**, **SDC**, http://links.lww.com/TP/B802). No additional comorbidities were identified as significant, and hazard ratios were very similar to the original models, confirming the reliability of the results.

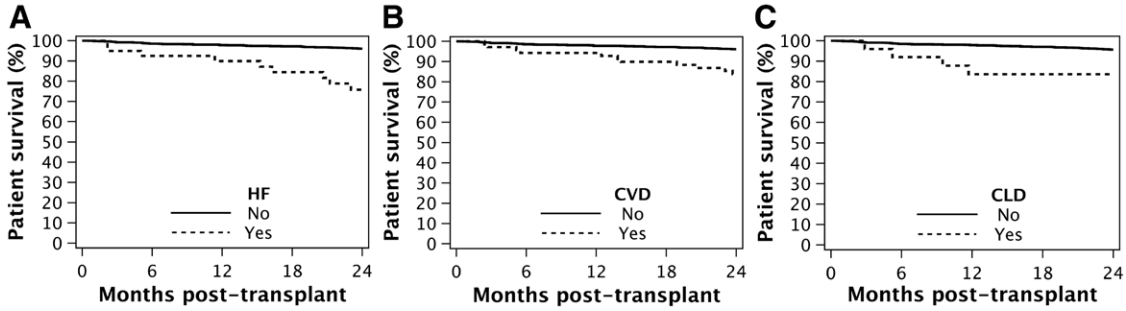

FIGURE 3. Kaplan-Meier curves for 2-y patient survival after deceased-donor kidney transplantation. A, Heart failure (HF). B, Cerebrovascular disease (CVD). C, Chronic liver disease (CLD).

TABLE 7.

Cox regression analysis for impact of comorbidity on 2-year transplant survival of living-donor kidney transplants

Variables	HR (95% CI)	*P*
Recipient comorbidity		
Heart failure	3.83 (1.15-12.81)	0.029
Diabetes	2.23 (1.03-4.81)	0.042
Other variables		
Time on dialysis, years		
<3	1 (reference)	
≥3	2.16 (1.13-4.11)	0.019
Recipient age (per 10 y)	1.01 (0.80-1.28)	0.926
Donor age (per 10 y)	1.03 (0.81-1.31)	0.828
HLA MM level		
1	1 (reference)	
2	0.76 (0.23-2.51)	0.657
3	0.74 (0.29-1.86)	0.520
4	0.67 (0.25-1.82)	0.428

CI, confidence interval; HLA MM, HLA mismatch; HR, hazard ratio.

DISCUSSION

In this national observational study, we have collected data prospectively on a wide range of comorbid conditions and identified those that predict poorer survival outcomes after kidney transplantation. Among DDKT recipients, PVD and obesity were associated with a 2- to 3-fold increased risk of graft failure within 2 years of transplantation, while the risk of death was 3- to 4-fold higher with HF, CVD, and CLD. For LDKT recipients, HF and diabetes were associated with significant detrimental effects on overall transplant survival, but longer follow up is required to determine the separate effects on graft and patient survival.

Among DDKT recipients, a history of PVD increased the risk of graft failure by 10.4% after adjusting for confounding factors, with the majority of graft failures occurring in the early postoperative period. PVD is typically diagnosed clinically by measuring the ankle-brachial pressure index (ABPI), and our results are in agreement with a US study of 819 patients, which reported a 2.77 times increased risk of graft failure for patients with a low ABPI (<0.9).[21] Preexisting PVD affecting the aorta or iliac arteries may complicate implantation of the kidney graft, resulting in difficult anastomoses, cholesterol emboli or hypoperfusion of the graft, and subsequent failure in the early postoperative period.[22,23] Our data showed a high incidence of technical operative issues as the cause of graft failure among PVD patients (42.9%). We also found that the addition of DGF to the regression model for DDKT graft survival reduced the effect of PVD and is thus a potential mediator of this effect. Despite being a high-risk group, patients with PVD still derive a significant survival benefit from transplantation compared with dialysis.[24,25] As such, a history of PVD should not preclude transplantation, but given the high risk of early complications, appropriate preoperative planning and informed consent of patients is crucial.

Obesity is an ongoing topic of controversy with regard to patient suitability for kidney transplantation. Some centers do not exclude patients with obesity, while others restrict access to the waiting list at specific BMI thresholds, which may differ considerably between centers, and even between clinicians within the same center.[26] Despite conflicting outcomes from early single-center studies, more recent meta-analyses have confirmed the detrimental effect of obesity on graft survival.[27-30] Our results are keeping with this evidence; with obesity conferring a 6% increased risk of graft failure among DDKT recipients. The mechanisms for this are unclear. There was a high incidence of acute rejection as a cause of graft failure among obese patients (44%) and this could be a potential cause for the higher risk of graft failure associated with obesity. Difficulties in achieving and maintaining the narrow therapeutic target concentrations of immunosuppressive drugs in obese patients have previously been reported.[31]

We found that HF was associated with a 15.9% higher risk of mortality after DDKT and 12.1% higher risk of transplant failure after LDKT. We acknowledge that in patients on dialysis, it can be difficult to make a clear distinction between HF and fluid overload; however, our findings demonstrate that a diagnosis of heart failure in the patient's record predicts poorer survival, irrespective of how the diagnosis was made or the exact pathophysiology. It is also noteworthy that although HF was identified as a significant risk factor, no effect was observed for IHD. Our findings concur with the results of a US study, which found that pretransplant impaired left ventricular systolic function (on single photon emission computed tomography [SPECT]) was associated with a significantly higher risk of both circulatory mortality and all-cause mortality after kidney transplantation, while cardiac ischemia (on SPECT) was not.[32] Our findings suggest that either IHD does not increase the risk of death within 2 years posttransplantation, or that current risk stratification of patients with IHD in the UK is effective.

CVD was associated with a 4.1% elevated risk of death among DDKT recipients. It is known that patients with ESRD have more severe carotid atherosclerosis than the general population and are at substantially greater risk of stroke.[33-35] A large US registry analysis demonstrated that transplantation reduced the risk of cerebrovascular events from 11.8% to 6.8% compared to patients remaining on the waiting list.[36] However, previous CVD remains a strong risk factor for further posttransplantation events and mortality.[35,37,38] Posttransplantation cerebrovascular events are associated with high mortality,[39] which is worse for hemorrhagic strokes (48%) compared with ischemic strokes (6%).[38] In a prospective randomised controlled trial including 1652 kidney transplant recipients (ALERT trial), the use of Fluvastatin did not reduce the incidence of cerebrovascular events or mortality.[38] Further trials are needed to assess the ability of therapies to reduce the risk of further cerebrovascular events and mortality in this high risk population.

CLD was independently associated with 5.6% increased risk of mortality within 2 years of DDKT. There is a paucity of published research regarding CLD in kidney transplant outcomes. Previous studies have focused on the role of hepatitis B- and C-related liver disease as predictors of increased mortality after kidney transplantation.[40-42] The present study is the first to demonstrate that CLD of any aetiology leads to reduced survival after DDKT. Further research is required to understand the underlying mechanisms.

Interestingly, a diagnosis of diabetes was identified as a risk factor for transplant failure among LDKT recipients, but not for DDKT recipients. The reason for this finding is unclear. Diabetes is a well-recognized risk factor for mortality after transplantation, primarily due to elevated cardiovascular risk.[43] It may be that this cardiovascular risk was actually accounted for by other comorbidity variables in the models for DDKT recipients, while in the LDKT cohort with a significantly lower prevalence of other comorbidities, diabetes may have served as more general marker of poorer outcomes. A recent large population cohort study in Australia and New Zealand demonstrated that patients with type 2 diabetes had significantly poorer survival after kidney transplantation, with the highest risk being among younger patients under the age of 40 years.[44] In our study, the LDKT population was significantly younger than the DDKT population and this may explain why diabetes was a significant risk factor in this population. The 5.6% higher risk of transplant failure among patients with diabetes (and 12% higher risk for patients with heart failure discussed previously) must be given due consideration in the context of LDKT, given the potential implications for both the recipient as well as the live donor.

A major strength of the present study is that it is a prospective and comprehensive analysis of a large cohort of transplant recipients from all UK transplant centers. The cohort included a large proportion of the national adult transplant population with a minimal amount of missing data, which adds to the reliability of the study. There are a number of limitations to this study. First, for practical reasons, we used relatively broad definitions for each comorbidity and were unable to distinguish between differing levels of severity or duration for each condition. All comorbidity data were collected at the time of transplantation when patients were recruited to the study. Therefore, we were unable to assess the progression or improvement of each condition after transplantation, and whether this impacted on outcomes. Second, it should be noted that the study population is largely of white ethnicity and thus conclusions with respect to other ethnic groups may be less certain. Third, due to the favorable survival outcomes of LDKT recipients, we were only able to analyse the composite outcome of transplant survival in this cohort, as there were too few events for separate analysis of graft and patient survival. Transplant survival (also known as graft survival not censored for death) is a commonly analysed end-point in the transplant literature, as it demonstrates the overall success of a transplant.[45,46] However, in the DDKT analysis, we found that this method masked the importance of several comorbidity risk factors that were found to be significant when analysing graft and patient survival separately. Therefore, it is important that we carry out separate graft and patient survival analyses in the LDKT cohort after longer follow-up time. Finally, the results from this study describe associations and no causation can be inferred.

This study quantifies the risks associated with specific comorbid conditions in the context of kidney transplantation. The findings can be utilised in everyday clinical practice to fully inform patients of their individual risks and outcomes, to inform future waitlisting and allocation policy, and also to guide further research into improving the outcomes of patients with specific comorbidities.

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